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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/684,440	10/15/2003	Rosanne M. Crooke	ISPH-0595US.P1 (ISIS.019C	4998

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EXAMINER	
BOWMAN, AMY HUDSON	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 05/30/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	10/684,440	CROOKE ET AL.
	Examiner	**Art Unit**
	Amy H. Bowman	1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 February 2006*.
2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.
3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6-8,14-17,22,25,30,32 and 40-59* is/are pending in the application.
4a) Of the above claim(s) *41-44 and 46-49* is/are withdrawn from consideration.
5)☐ Claim(s) _____ is/are allowed.
6)☒ Claim(s) *6-8,14-17,22,25,30,32,40,45 and 50-59* is/are rejected.
7)☐ Claim(s) _____ is/are objected to.
8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.
10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a)☐ All b)☐ Some * c)☐ None of:
1.☐ Certified copies of the priority documents have been received.
2.☐ Certified copies of the priority documents have been received in Application No. _____.
3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)	4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)	5) ☐ Notice of Informal Patent Application (PTO-152)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/9/2006*.	6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed 2/27/2006 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 8/26/2005 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Claims 6-8, 14-17, 22, 25, 30, 32, and 40-59 are pending in the application.

Applicants cannot file an RCE to obtain continued examination on the basis of claims that are independent and distinct from the claims previously claimed and examined as a matter of right (i.e., applicant cannot switch inventions). See 37 CFR 1.145. Any newly submitted claims that are directed to an invention that is independent and distinct from the invention previously claimed will be withdrawn from consideration and not entered. An RCE is not the filing of a new application (see MPEP 706.07(h)).

Newly submitted claims 41-44 and 46-49 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Applicant elected antisense oligonucleotide SEQ ID NO: 23 in applicant's response filed 1/3/2005. Applicant has now introduced claims drawn to another target region, as well as to antisense oligonucleotide SEQ ID NO: 11. These claims are drawn to a non-elected invention.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 41-44 and 46-49 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 2/27/2006 has been entered.

Response to Arguments—35 USC § 112, first paragraph

Applicant's arguments with regards to the 35 U.S.C. 112, 1st paragraph rejection of record are addressed in the new 35 U.S.C. 112, 1st paragraph rejection below.

Response to Arguments—35 USC § 102

Claims 6, 7, 14, 25, 30 and 32 stand rejected under 35 U.S.C. 102(b) as being anticipated by Rouy et al. (WO 99/35241), for the reasons of record explained in the office action mailed 8/26/2005.

Claims 4, 5, 9-13, 33, 35 and 37-39 have been cancelled by applicant, obviating the rejection against these claims.

Applicant argues that the instant limitations "inhibits the expression of apolipoprotein(a) mRNA by at least 10%" and "does not substantially inhibit plasminogen", which are not taught by Rouy et al. Applicant argues that Rouy et al. does not disclose any antisense oligonucleotide that is capable of inhibiting the expression of apolipoprotein(a) mRNA.

Contrary to applicant's arguments, Rouy et al. teaches a method comprising administering an apolipoprotein(a) antisense oligonucleotide to a cell or tissue and teach that such antisense nucleic acids are capable of specifically hybridizing with a nucleic acid encoding apolipoprotein (a) and that down regulation of the target gene expression can be achieved. Rouy et al. teach that any length of antisense sequence is suitable for this method as long as it is capable of down-regulating or blocking expression of apolipoprotein (a), but preferably the antisense sequence is at least 20 nucleotides in length (see page 23). Rouy et al. further teach methods for determining whether a compound can inhibit a disease or disorder such as cardiovascular disease, atherosclerosis or coronary artery disease. Contrary to applicant's assertions, Rouy et al. does not need to exemplify the teachings in order to anticipate the instant invention.

Applicant relies upon the instant limitations "inhibits the expression of apolipoprotein(a) mRNA by at least 10%" and "does not substantially inhibit plasminogen" although the instant specification does not teach any structural characteristic that would result in such activity. The language relied upon by applicant does not limit the structure of the claimed invention. Rouy et al. teach a method comprising each of the structural limitations of the instant claims and is therefore considered to necessarily anticipate the invention.

Therefore, the instant invention is anticipated by Rouy et al.

Response to Arguments—35 USC § 103

Claims 6-8, 14-17, 22, and 25, stand rejected under 35 U.S.C. 103(a) as being unpatentable over Morishita et al., in view of Frank et al., and further in view of Baracchini et al. for the reasons of record set forth in the office action mailed 1/26/05 and maintained in the office action mailed 8/26/2005.

Claims 4, 5, 9-13, and 18 have been cancelled by applicant, obviating the rejection against these claims.

Applicant argues that the addition of the limitation "antisense oligonucleotide does not substantially inhibit plasminogen" renders the instant rejection improper because the cited references neither alone nor in combination teach or suggest all of the limitations.

Contrary to applicant's argument, Morishita et al. teaches ribozyme oligonucleotides targeted against apolipoprotein(a) that selectively inhibit apolipoprotein(a) but not plasminogen gene expression. Frank et al. teach the usage of a full-length apolipoprotein(a) antisense RNA to inhibit apolipoprotein(a) synthesis (see abstract, figure 1). Antisense transduction caused a significant reduction in apolipoprotein(a) secretion (see results). As evidenced by Baracchini et al., it was known in the art at the time the invention was made to design and utilize antisense oligonucleotides to inhibit target gene expression in a sequence specific manner. Therefore, it would have been obvious to make an antisense oligonucleotide, in the size range and with the modifications taught by Baracchini et al., targeted to apolipoprotein(a), as taught by Frank et al. Additionally, it would have been obvious to target apolipoprotein(a) because Morishita et al. teach ribozyme oligonucleotides targeted against apolipoprotein(a) that selectively inhibit apolipoprotein(a) but not plasminogen gene expression, which are also sequence specific inhibitors of target gene expression. Since it was known in the art to selectively inhibit apolipoprotein(a) expression but not plasminogen expression with a ribozyme, one would have been motivated to do so with an antisense oligonucleotide as well since Baracchini et al. teach that antisense oligonucleotides are capable of modulating expression of genes implicated in diseases (see column 4).

Applicant argues that the declaration pursuant to 37 CFR § 1.131 filed 5/25/05 establishes conception of the present invention prior to the cited Frank reference. Applicant argues that therefore Frank et al. should not constitute prior art under 35 U.S.C. 103(a). As explained in the "Priority" section below, applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

In the instant case, the effective filing date is determined to be that of the instant application 10/684,440, which has an effective filing date of 10/15/2003. The instant claims do not receive the benefit of 09/923,515 and 60/475,402 because the instant claim limitation wherein the antisense oligonucleotide does not substantially inhibit plasminogen is not supported by the specification or claims of the previously mentioned parent applications.

Applicant points to page 4, lines 16-30; page 11, line 26 to page 12, line 33; and page 52, line 28 to page 53, line 18 of application 09/923,515 for support for the instant claim amendments. However, upon review of application 09/923,515, support for the instant limitation "does not substantially inhibit plasminogen" is not evident.

Thus, the instant application is accorded an effective filing date of 10/15/2003.

Therefore, the declaration pursuant to 37 CFR § 1.131 filed 5/25/05 is considered ineffective. The Frank et al. reference was published more than one year prior to the instant effective filing date, therefore presenting a statutory bar that cannot be overcome by a 1.131 declaration.

Double Patenting

Claims 6-8, 14-17, 22, 25, 30, and 32 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the claims of copending application 10/485,113 for the reasons of record set forth in the office action mailed 1/26/2005. Claims 4, 5, 9-13, 18, and 33-35 have been cancelled by applicant, obviating the rejection against these claims. Applicant has requested to defer addressing this rejection until the claims are otherwise in condition for allowance.

Claims 6-8, 14-17, 22, and 25 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the claims of copending application 09/923,515 for the reasons of record set forth in the office action mailed 1/26/2005. Claims 4, 5, 9-13, 18, and 33 have been cancelled by applicant, obviating the rejection against these claims. Applicant has requested to defer addressing this rejection until the claims are otherwise in condition for allowance.

New Objections/Rejections

Claim Objections

Claims 6-8, 14-17, 22, 25, 30, 32, 40, 45, and 50-59 are objected to because of the following informalities: None of the instantly listed claims have a period after the claim number. Appropriate correction is required.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

In the instant case, the effective filing date is determined to be that of the instant application 10/684,440, which has an effective filing date of 10/15/2003. The instant claims do not receive the benefit of 09/923,515 and 60/475,402 because the instant claim limitation wherein the antisense oligonucleotide does not substantially inhibit plasminogen is not supported by the specification or claims of the previously mentioned parent applications.

Applicant points to page 4, lines 16-30; page 11, line 26 to page 12, line 33; and page 52, line 28 to page 53, line 18 of application 09/923,515 for support for the instant claim amendments. However, upon review of application 09/923,515, support for the instant limitation "does not substantially inhibit plasminogen" is not evident.

Thus, the instant application is accorded an effective filing date of 10/15/2003.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 6-8, 14-17, 22, 25, 30, 32, 40, 45, and 50-59 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention because it is unclear what is meant by the terminology "substantially inhibit". The instant specification does not define the term "substantially". One of ordinary skill in the art would not understand the metes and bounds of the word "substantially" to be able to envision the scope of the instant claims.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 6-8, 14-17, 22, 25, 30, 32, 40, 45, and 50-59 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

Claims 6-8, 14-17, 22, 25, 30, 32, 40, 45, and 50-59 are directed to methods of utilizing an antisense oligonucleotide to inhibit the expression of apolipoprotein(a). The newly added limitation "wherein the antisense oligonucleotide does not substantially inhibit plasminogen" is not supported by the instant specification. Therefore, this newly added claim limitation constitutes new matter. This limitation was first introduced in the amendment to the claims filed 2/27/2006. Additionally, there is no support for this claim limitation in the claimed priority documents.

Applicant points to the claims as originally filed for support and asserts that support can be found throughout the instant specification. Upon a review of the instant specification, the only potential support for the newly added limitation is found in claim 18 of the originally filed claims. This claim recites that the compound preferentially binds to a nucleic acid sequence of apolipoprotein(a) and does not bind, or binds weakly to a nucleic acid sequence encoding plasminogen. Applicant has not taught a nexus between the originally filed limitation of "binding weakly" and the instant limitation of "does not substantially inhibit". The limitation of binding weakly to plasminogen is not considered support for not substantially inhibiting plasminogen. It is not understood what is meant by "binding weakly" in the originally filed claims to be able to correlate this language to an inhibitory guideline. Additionally, the instantly recited language "substantially" does not appear in the originally filed specification or claims and is considered new matter. The instant specification does not offer any support for "does not substantially inhibit plasminogen" and does not give any guideline or definition of how to interpret "substantially".

Furthermore, originally filed claim 33 recites that the antisense compound has at least 3 mismatches to human plasminogen. It is unclear whether "at least 3 mismatches" would cause weak binding, as recited in originally filed claim 18.

Additionally, any negative limitation or exclusionary proviso must have basis in the original disclosure. The mere absence of a positive recitation is not basis for an exclusion (see MPEP 2173.05(i)).

A review of the specification does not reveal support for where this claim limitation is found. Should applicant disagree, applicants are encouraged to point out with particularity by page and line number where such support might exist.

Claims 6-8, 14-17, 22, 25, 30, 32, 40, 45, and 50-59 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The invention of the above claims is drawn to a method of inhibiting the expression of apolipoprotein(a) in a cell or tissue comprising contacting the cell or tissue with an antisense oligonucleotide targeted to SEQ ID NO: 4, as well as a method of treating a human having a disease or condition treatable by the reduction of apolipoprotein(a) via administering an antisense oligonucleotide targeted to SEQ ID NO: 4, wherein said antisense oligonucleotide does not substantially inhibit plasminogen.

The claims broadly read on a method involving utilizing an antisense oligonucleotide targeted to SEQ ID NO: 4 that does not substantially inhibit plasminogen. Although the specification discloses antisense oligonucleotides targeted to apolipoprotein(a) (SEQ ID NO: 4), the specification does not sufficiently describe how to determine which antisense oligonucleotides will inhibit apolipoprotein(a) (SEQ ID NO: 4) without substantially inhibiting plasminogen. The skilled artisan would not be able to envision the genus claimed of antisense oligonucleotides such that the skilled artisan would recognize that the applicant was in possession of the claimed genus at the time of filing.

The skilled artisan would not be able to envision which antisense oligonucleotides would inhibit apolipoprotein(a) (SEQ ID NO: 4) mRNA by at least 10% without substantially inhibiting plasminogen without undue experimentation.

MPEP 2163 states in part, "An adequate written description of a chemical invention also requires a precise definition, such as by structure, formula, chemical name, or physical properties, and not merely a wish or plan for obtaining the chemical invention claimed. See, e.g., *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 927, 69 USPQ2d 1886, 1894-95 (Fed. Cir. 2004).

Additionally, applicant has not adequately described a structure that would lead one of skill in the art to be able to envision which antisense oligonucleotides are "specifically hybridizable" with the target sequence. The instant specification defines "specifically hybridizable" as terminology to indicate a sufficient degree of precise pairing or complementarity over a sufficient number of nucleobases such that stable and specific binding occurs between the oligonucleotide and a target nucleic acid. The specification does not teach a structural guideline that would lead one of skill in the art to be able to envision the genus of antisense oligonucleotides that have a "sufficient" degree of precise base pairing over a "sufficient" number of nucleobases to achieve the desired effect of stable and specific binding.

Thus, the instantly claimed invention cannot be said to have been adequately described in a way that would convey with reasonable clarity to those skilled in the art that, as of the filling date sought, applicant was in possession of the claimed invention because the specification does not provide a description of the genus of antisense oligonucleotides that inhibit apolipoprotein(a) (SEQ ID NO: 4) without substantially inhibiting plasminogen.

Claims 30, 32, 45, 50-56, 58 and 59 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a treatment method via intraperitoneal injection of an apolipoprotein(a) antisense oligonucleotide, does not reasonably provide enablement for the treatment of the broad scope of instantly recited diseases or disorders via any delivery means. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The invention of the above claims is drawn to a method of treating a human having a disease or condition treatable by the reduction of apolipoprotein(a) via administering an antisense oligonucleotide targeted to SEQ ID NO: 4, wherein said antisense oligonucleotide does not substantially inhibit plasminogen.

The declaration pursuant to 37 CFR 1.132 filed on 2/27/2006 teaches the intraperitoneal injection of an antisense oligonucleotide (SEQ ID NO: 11) to transgenic mice, wherein the antisense oligonucleotide is 100% complementary to instant SEQ ID NO: 4, apolipoprotein(a).

The instant claims do not recite a specific mode of administration of the antisense oligonucleotide. Although the declaration teaches intraperitoneal injection, applicant is not enabled for the broad scope of any means of delivery.

Additionally, although applicant has demonstrated a reduction in apolipoprotein(a) protein levels, these teachings do not enable applicant for the scope of treating a human for the broad scope of instantly recited diseases or disorders. Specifically, applicant has not shown how the reduction of apolipoprotein(a) expression results in a treatment effect for the broad scope of any cardiovascular disorder, atherosclerosis, hypercholesterolemia, coronary artery disease, or any combination thereof.

Applicant asserts that the declaration filed provides journal articles showing that the transgenic mouse model is used by those of ordinary skill in the art to investigate the involvement of apolipoprotein(a) in the progression of human atherosclerosis. Upon review of the literature, it is agreed that a transgenic mouse model is accepted as a means of studying the involvement of apolipoprotein(a) in the progression of human atherosclerosis. However, this does not enable applicant for treatment of the diseases or disorders claimed because applicant has not demonstrated such a treatment effect regarding the specific diseases or disorders via administering an antisense oligonucleotide and certainly hasn't demonstrated an effect that would demonstrate treatment of such a wide array of diseases or disorders. The art cited by applicant is silent as to such effects of an antisense oligonucleotide.

The instant specification does not teach how to target the claimed antisense oligonucleotide via any means of delivery other than intraperitoneal injection to cells or tissues *in vivo*. Furthermore, upon inhibition of the apolipoprotein(a) target, the instant specification does not teach a resultant treatment of any cardiovascular disorder, atherosclerosis, hypercholesterolemia, coronary artery disease, or any combination thereof, as instantly claimed.

The specification does not offer guidance to resolve the known unpredictability in the art associated with means of *in vivo* delivery and treatment effects provided by the instantly claimed method.

The references cited herein illustrate the state of the art for therapeutic *in vivo* applications using antisense compounds. Green et al. ((Antisense Therapy in Human Disease, Vol. 191, No. 1, 2000) state that "[i]t is clear from the evolution of antisense technology from a laboratory research tool into a mechanism for designing active and effective drugs is far from complete. Although there is little doubt that systemically administered antisense [oligonucleotides] can inhibit the expression of specific genes in patients, the effectiveness of such therapy in modifying the course of a particular illness has not yet been established. In addition, toxicity in humans appears more problematic than might be predicted based on preclinical studies in rodents. Clearly, additional work must be done to unravel the complex problems associated with drug delivery, mRNA targeting and aptameric, nonantisense effects".

As evidenced by Green et al., the inhibition of gene expression of a specific gene does not necessarily correlate to modifying the course of a particular illness. Although applicant has demonstrated successful inhibition of the apolipoprotein(a) (SEQ ID NO: 4) target *in vivo* in transgenic mice, applicant has not demonstrated a treatment effect commensurate with the scope of the instant claims.

The problems with efficient delivery of antisense oligonucleotides to cells has been addressed by Jen et al. (Stem Cells, 2000, 18:307-319), who states that "[o]ne of the major limitations for the therapeutic use of AS-ODNS ... is the problem of delivery.... presently, some success has been achieved in tissue culture, but efficient delivery for *in vivo* animal studies remains questionable." Jen et al. concludes that "[g]iven the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive (see p 315, second column)."

Since delivery remains a challenge in the field of antisense oligonucleotide therapeutics, successful delivery of an antisense oligonucleotide via intraperitoneal injection does not enable applicant for the broad scope of any means of delivery.

As outlined above, it is well known that there is a high level of unpredictability in the antisense art, for therapeutic *in vivo* applications. The scope of the claims in view of the specification as filed together do not reconcile the unpredictability in the art to enable one of skill in the art to make and/or use the claimed invention, namely a broad therapeutic effect of an antisense oligonucleotide targeted to apolipoprotein(a) (SEQ ID NO: 4).

Given the teachings of the specification as discussed above, one skilled in the art could not predict *a priori* whether introduction of antisense oligonucleotides *in vivo* by the broadly disclosed methodologies of the instantly claimed invention, would result in successful treatment of the broad genus of instantly recited diseases or disorders. Without further guidance, one of skill in the art would have to practice a substantial amount of trial and error experimentation, an amount considered undue and not routine, to practice the instantly claimed invention.

Claim Rejections - 35 USC § 102 or 103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 6, 14, 16, 22, 25, 40, and 57 are rejected under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Ben-David et al. (US 6,573,050 B1).

The invention of the above claims is drawn to a method of inhibiting apolipoprotein(a) (SEQ ID NO: 4) expression comprising contacting a cell or tissue with an antisense oligonucleotide 12 to 30 nucleobases in length targeted to SEQ ID NO: 4, wherein said oligonucleotide does not substantially inhibit plasminogen and inhibits the expression of apolipoprotein(a) mRNA by at least 10%. The invention is further drawn to modifications of the oligonucleotide.

Ben-David et al. teach a method of a method of treating melanoma cells via contacting said cells with an antisense oligonucleotide so that target gene expression is reduced. The antisense oligonucleotide taught by Ben-David et al. is 20 nucleotides in length and is DNA. Ben-David et al. teach phosphorothioate linkages (see column 6). Ben-David et al. teach antisense oligonucleotides designed to target the coding region or the target.

The antisense oligonucleotide taught by Ben-David et al. is fully complementary to "a portion" of SEQ ID NO: 4. Specifically, the antisense oligonucleotide taught by Ben-David et al. is fully complementary to nucleotides 175-184 of instant SEQ ID NO: 4 (see nucleotides 3-12 of SEQ ID NO: 5 of Ben-David et al.). The instant claim language "fully complementary to a portion" requires full complementarity to any sized portion of instant SEQ ID NO: 4, even at a single base. Additionally, the antisense oligonucleotide of Ben-David et al. comprises at least 3 mismatches as compared to the nucleotide sequence encoding human plasminogen.

Although Ben-David et al. do not disclose the antisense oligonucleotide of their method to inhibit the expression of apolipoprotein(a), as instantly recited, the antisense oligonucleotide of Ben-David et al. meets all of the structural requirements of the instant claims and would therefore be expected to inhibit the expression of apolipoprotein(a) (SEQ ID NO: 4) by at least 10%, as instantly recited.

Additionally, since the antisense oligonucleotide of Ben-David et al. meets each of the structural limitations of the instant claims, the oligonucleotide would necessarily "not substantially inhibit plasminogen", as instantly claimed. As explained in the 35 U.S.C. 112, first paragraph rejection above, the specification does not disclose how to determine which antisense oligonucleotides would inhibit apolipoprotein(a) expression without substantially inhibiting plasminogen. Since there has not been a structural characteristic imparted by this limitation of the claim, the oligonucleotide of Ben-David et al. would necessarily meet this limitation.

See, for example, MPEP § 2112, which states "[w]here applicant claims a composition in terms of a function, property or characteristic and the composition of the prior art is the same as that of the claim but the function is not explicitly disclosed by the reference, the examiner may make a rejection under both 35 U.S.C. 102 and 103, expressed as a 102/103 rejection. 'There is nothing inconsistent in concurrent rejections for obviousness under 35 U.S.C. 103 and for anticipation under 35 U.S.C. 102.' In re Best, 562 F.2d 1252, 1255 n.4, 195 USPQ 430, 433 n.4 (CCPA 1977). This same rationale should also apply to product, apparatus, and process claims claimed in terms of function, property or characteristic. Therefore, a 35 U.S.C. 102/103 rejection is appropriate for these types of claims as well as for composition claims."

Therefore, the instant invention is anticipated or obvious over Ben-David et al.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy H. Bowman whose telephone number is 571-272-0755.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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